REMARKS

Introductory Comments

Claims 1-14 and 16 were variously rejected in the Office Action under reply under (1) 35 U.S.C. §112, second paragraph (claims 8-14); and (2) 35 U.S.C. §103(a) (claims 1-14 and 16). These rejections are traversed and believed to be overcome for reasons discussed below.

Applicants acknowledge with appreciation the withdrawal of all of the previous rejections.

Overview of the Amendments

The application has been amended to provide an Abstract of the Disclosure, as requested by the Office. Additionally, claims 1-14 and 16 have been canceled herein and replaced with new claims 17-29. Cancellation of the previous claims is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to pursue the subject matter of the canceled claim in another application.

New claims 17-29 find support in the previous claims, as well as throughout the specification at, e.g., page 2, lines 5-13; page 3, lines 8-15; page 3, line 28 through page 4, line 1; page 4, lines 4-5; and page 4, lines 10-13; page 4, line 29 through page 5, line 3.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Office rejected claims 8-14 under 35 U.S.C. §112, second paragraph, stating "it is unclear to whom or to what the composition is being administered." Office Action, page 4. Applicants have inserted the term "mammalian subject" into new claim 29. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103(a)

The Office rejected claims 1-14 and 16 under 35 U.S.C. §103(a) as unpatentable over Granoff et al., *Infect. Immun.* (1997) 65:1710-1715 ("Granoff-1") or Costantino et al., *Vaccine* (1992) 10:691-698 ("Costantino") and Milagres et al., *FEMS Immunol. Med. Microbiol.* (1996) 13:9-17 ("Milagres"), in view of Granoff et al., *Vaccine* (1993) 11:S46-S51 ("Granoff-2) or Blake et al., U.S. Patent No. 6,451,317 ("Blake"). The Office asserts Granoff-1 and Costantino teach an NmC-CRM_{197} conjugate vaccine with aluminum hydroxide and a method of inducing an immune response to NmC. Granoff-1 is also alleged to suggest "the use of their conjugate vaccine 'in combination' with other vaccines." Office Action, page 5. The Office acknowledges Granoff does not teach the use of NmB vesicles but cites Milagres as teaching NmB outer membrane vesicles in an NmB and NmC vaccine. Granoff-2 is said to teach that NmB OMP displays adjuvant activity. Similarly, Blake is cited for disclosing "the use of meningococcal OMV as an adjuvant capable of direct T cell stimulation, or immunopotentiation." Office Action, page 5. However, applicants do not agree that the cited combination renders the present claims obvious.

Section 2142 of the MPEP sets forth the following basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify the references or combine reference teachings; (2) there must be a reasonable expectation of success (for the modification); and (3) the prior art references must teach or suggest all of the claim limitations. Furthermore, the teaching or suggestion and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. The Office has failed to satisfy these criteria. Applicants submit there is no suggestion or motivation to combine the references as proposed by the Office.

In particular, all of the present claims pertain to immunogenic compositions comprising (1) an NmC oligosaccharide conjugated to a carrier and (2) NmB proteoliposomic vesicles, and uses of these compositions. None of the cited art, either alone or in combination, teaches or suggests the claimed invention. Specifically, Granoff-1 pertains to studies to determine the ability of the adjuvant MF59 to enhance the immunogenicity of NmC and *Haemophilus influenzae* type b (Hib) conjugate vaccines.

The paper nowhere discusses the use of MF59 or any other adjuvant, for that matter, with NmC/NmB combination vaccines. In fact, the paper does not even discuss NmB. The Examiner focuses on a statement at the end of the paper that an adjuvant might permit the use of "multicomponent PS-protein conjugate vaccines given alone or in combination with other vaccines." Granoff-1, page 1714, second column. However, this statement sheds absolutely no light on what those other vaccines might be. In the absence of more guidance, this statement can at best be considered an invitation to experiment and such is not a proper basis for an obviousness rejection.

Similarly, Costantino pertains to a meningococcus A and C conjugate vaccine. Again, the authors do not describe or suggest using such a vaccine with an NmB protein, let alone an NmB proteoliposomic vesicle preparation. In fact, Costantino teaches that in order for an NmB vaccine to be efficacious, the polysaccharide must be conjugated to CRM_{197}. Costantino, at page 691 states:

> In the case of group B *N. meningitidis*, a vaccine is not yet available because the purified capsular polysaccharide is not immunogenic in humans. Poor immunogenicity in children is a limitation shared by many polysaccharides as a consequence of their T-independent character. This drawback has usually been overcome by coupling immunogenic proteins to polysaccharides or oligosaccharides to convert these antigens to a T-dependent form...This approach seems able to overcome also the poor immunogenicity of meningococcus B polysaccharide.

Thus, Costantino actually teaches away from providing an NmB component as proteoliposomic vesicles.

Milagres fails to provide the missing link. Milagres does not describe or suggest the use of NmC oligosaccharides conjugated to a carrier. Milagres administered an NmC purified capsular polysaccharide and an NmB outer membrane vesicle (OMV) preparation to mice. Milagres' NmC vaccine components are not analogous to applicants' NmC oligosaccharides. Particularly, as explained at page 4, lines 4-9 of the application, the NmC oligosaccharides used by applicants are polysaccharide fragments that include repeating units, preferably about 12 to 22 repeating units. The NmC polysaccharide vaccine used by Milagres is not the same as, or analogous to, applicants' oligosaccharide

Not in broader claims

NmC component. As explained at page 1, lines 19-21 of the present application, the NmC polysaccharide vaccine is not effective in infants and young children.

Finally, both Granoff-2 and Blake pertain to Hib polysaccharide vaccines conjugated to an outer membrane protein complex of NmB. The NmB component acts as an adjuvant to enhance the immune response to the Hib component. Contrary to the Action's assertion, Blake actually states that the mechanisms by which Neisserial porins act as adjuvants is unknown. See, column 3, lines 19-34. There is no suggestion in Granoff-2 or Blake to use the NmB component as an immunogen itself. There is absolutely no suggestion in either of Granoff-2 or Blake that the NmB component of the Hib polysaccharide complex would function to induce an immunologic response against NmB.

None of the cited art discloses or suggests combination vaccines using both an NmC oligosaccharide conjugated to a carrier and NmB proteoliposomic vesicles. The cited combination gives neither a suggestion nor an expectation of success for the use of such a combination vaccine, and both must be present in the prior art in order for the Patent Office to make out a *prima facie* case of obviousness. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). It is well known that mixtures of immunogens can fail to be as effective as individual components due to physical interactions of the individual immunogens which might result in altered conformation, aggregation or precipitation. Immunological dominance or competition between component immunogens is also known to occur. Finally, the FDA requires that the efficacy of new mixtures be shown even if the efficacy of the individual components or other mixtures using the individual components has been demonstrated, further evidencing the unpredictable results obtained with new mixtures.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified, does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Without a suggestion to modify the references evident in the prior art as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction

of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, the rejection of the claims over the stated combination should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

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Respectfully submitted,

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